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Attenuation of Exercise Conditioning by Low Dose Beta-Adrenergic Receptor Blockade

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Because it has been shown that high doses of propranolol (40 to 80 mg orally, four times daily) markedly attenuate cardiovascular response to exercise training in healthy subjects, the effects of lower doses of this nonselective beta-adrenergic receptor antagonist on the conditioning response were investigated. Twelve normal men underwent maximal treadmill testing before and after a 6 week intensive exercise program. After an initial test, six men were randomized in a paired fashion to receive low dose propranolol and the others received no drug. The average propranolol dose ± standard error was 22 ± 4 mg four times daily, and the average decrease in maximal heart rate due to propranolol was 32 ± 4 beats/min. Both groups trained at comparable intensities. At the end of the training period, propranolol was stopped and testing was repeated so that the effect of beta-receptor blockade was no longer present but the training effects still persisted. Maximal oxygen consumption increased in control subjects from 47.5 ± 1.1 to 51.4 ± 0.4 ml/kg per min ($p < 0.05$) but was unchanged in those receiving propranolol (47.2 ± 1.9 versus 47.4 ± 1.5). Exercise duration increased in both groups but the increment was greater in the control group (+2.4 versus +1.1 min, $p < 0.05$).

It is concluded that low level beta-receptor blockade attenuates cardiovascular conditioning in normal subjects in exercise training programs. High levels of sympathetic stimulation during training appear to be important, if not essential, to the conditioning process.

Previous work by our group (1) has demonstrated that high grade, nonselective blockade of beta-adrenergic receptors in normal men results in a markedly attenuated response to aerobic conditioning. This finding may have implications for many conditioning programs for prevention or therapy of cardiac disease, because use of beta-adrenergic receptor blocking drugs is quite common.

Many individuals undergoing exercise training may be taking less than maximal doses of beta-adrenergic receptor blocking drugs. Accordingly, we have extended our studies to normal subjects exposed to low levels of nonselective receptor blockade. We have evaluated the effects of submaximal blockade on aerobic conditioning and compared the training response to our previous results in studies that utilized maximal beta-adrenergic receptor blockade. Twelve healthy, sedentary, male volunteers were studied before, during and after an intensive 6 week, aerobic exercise program. Six subjects received no therapy and six received 20 to 30 mg of propranolol, four times daily, a dose designed to afford partial beta-blockade. Effects of the conditioning program were compared in the two groups by evaluating treadmill performance when no drug effect was present before and after training.

Methods

Study group. Twelve male volunteers, aged 22 to 34 years, were recruited to participate in the study. None had a history of cardiac or pulmonary disease or hypertension. All were nonsmokers and had not exercised regularly for at least 6 months before the study. The men had no evidence of cardiovascular or pulmonary disease by physical examination. No attempt was made to blind either ourselves or the participant, because in our prior study (1) in which we did attempt double blinding, it was obvious to investigators

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and most participants whether the subjects were taking medication.

Exercise protocol. Treadmill exercise testing was carried out after the subjects had abstained from alcohol for at least 72 hours and were in a fasting state for at least 12 hours. A supine electrocardiogram, heart rate (average of 10 recorded beats) and blood pressure were recorded after a 10 minute rest period. Graded maximal treadmill testing was then performed on a Quinton treadmill, model 1849C, using 2 minute stages. The protocol was designed so that the estimated total oxygen consumption was increased by 7 ml/kg per min at each of the first three stages, and by 3.5 ml/kg per min in each stage thereafter. Exercise was continued to exhaustion. The telemetered electrocardiogram was continuously monitored on an oscilloscope. Blood pressure by cuff sphygmomanometry, heart rate and electrocardiogram were recorded during the last 10 seconds of each minute of exercise, and for 5 minutes after exercise.

Expired gases were collected using a Collins 13 liter mouthpiece fitted to a Koegel valve. To measure ventilation, expired air was directed through a hot-wire anemometer into a mixing chamber. Expired carbon dioxide (CO_2) and oxygen (O_2) were measured by continuous sampling from the mixing chamber, using a Beckman LB-2 CO_2 analyzer and a fuel cell O_2 analyzer. Outputs from these analyzers were monitored on-line by a Micronova computer (Data General Corporation). Every 30 seconds during exercise, printouts were obtained of minute ventilation, oxygen consumption and carbon dioxide production.

Propranolol protocol. After a preliminary screening exercise test to assess suitability for inclusion in the study, each subject underwent a control treadmill test before exercise training or drug administration was begun (Test I). After Test I, participants were paired according to maximal oxygen consumption and randomly (coin toss) assigned to the control or drug group. The group randomized to receive the propranolol therapy were given sufficient doses of the drug to produce submaximal blockade. In our previous work in normal men (1), high grade beta-adrenergic receptor blockade with plasma levels in excess of 100 ng/ml resulted in decreases in maximal exercise heart rate of 59 ± 3 beats/min. We attempted to attain 50% submaximal beta-blockade, defined as a decrease of 30 beats/min in the maximal exercise heart rate attained by subjects during Test I. We initially gave propranolol (20 mg every 6 hours) to six subjects. The dosage was increased, if necessary, to attain a reduction of 30 beats/min in maximal heart rate on treadmill testing during the subsequent week. Before the treadmill test performed for dosage adjustment, blood samples were drawn for measurement of the plasma concentration of propranolol using the method of Aarons et al. (2). After dosage adjustment, a second set of measurements during treadmill exercise was performed (Test II). Both groups then began a 6 week program of high intensity exercise conditioning involving both supervised and unsupervised sessions.

Exercise training. Supervised sessions were held three times per week and utilized telemetry monitoring. Each session began with 5 minutes of stretching and warm-up exercises. This was followed by 8 minutes of continuous exercise on each of three devices: motor-driven treadmill, bicycle ergometer and steps (repeated step-ups utilizing a single step of fixed height). One or two minutes of rest was allowed between the different modes of exercise. Average steady state heart rate was recorded for each mode of exercise. A 20 minute run was undertaken after exercise on the devices. Unsupervised sessions were scheduled on 2 additional days per week, with subjects monitoring and reporting their own steady state pulse rate during 30 to 40 minutes of continuous running or bicycling. Compliance with medication was documented by weekly pill counts and by a propranolol blood level obtained randomly, 6 hours after a dose during the training. All subjects were required to exercise at or above a minimal heart rate that was 75% of the maximal heart rate attained during treadmill exercise at Test I for the control group or Test II for the drug group. The actual physical work performed was essentially identical for each pair of subjects whether in the control or propranolol group.

At the end of the sixth week of training, a third treadmill test (Test III) was performed in the drug group without interrupting their training schedule. After this test, no further drugs were administered and both the drug and control groups continued to exercise for 3 days while residual stores of the drug were metabolized. Both groups then underwent final treadmill testing (Test IV).

Statistical analysis. Comparisons of the mean changes within the control group were done by Student's *t* test for paired data. Changes within the drug group were assessed by two-way analysis of variance using the Student-Newman-Keul's test for multiple comparisons with a probability [p] value less than 0.05 considered to be significant. Comparison of the mean difference between the placebo and propranolol groups was accomplished by an unpaired, two-tailed *t* test. Results are reported as mean values ± standard error.

Results

Description of subjects on entry. Table 1 compares the control and drug groups on entry into the study. No significant differences were found between the groups with respect to age, weight, initial maximal oxygen consumption or treadmill exercise duration.

Achievement of submaximal beta-blockade. Five of six subjects initially received 20 mg of propranolol every 6 hours, and remained at that dose during the exercise period. One subject's dose was increased to 30 mg every 6 hours

Table 1. Comparison of Control and Propranolol Groups at Entry Into Study

	Control	Propranolol
Age (yr)	25.4 ± 1.3	26 1 ± 1.2
Weight (kg)	77.5 ± 7.6	79.8 ± 4.7
$\dot{V}O_2$ max (ml/kg per min)	47.5 ± 1.1	47.2 ± 1.9
Exercise duration (min)	18.3 ± 0.7	17 9 ± 0 8

Values are mean ± standard error. Differences between the groups are not significant. $\dot{V}O_2$ max = maximal oxygen consumption.

to attain the desired decrease in maximal exercise heart rate. The mean decrease in maximal exercise heart rate during submaximal beta-blockade was 32 ± 4 beats/min.

Compliance with medication and training. Compliance with the prescribed dosage schedule was confirmed by weekly counts of pill supplies, by observation of heart rates attained during exercise and by measured blood levels of propranolol. Table 2 lists the measured plasma trough levels in the drug group obtained before Tests II and III. A spot-check plasma level was also randomly obtained during the training period and agreed with the other levels.

Compliance with the exercise protocol was excellent in both the control and drug groups, with each group participating in 92% of all prescribed training sessions. Intensity of the training was similar and not statistically different for both groups, with steady state maximal heart rates during the monitored sessions at 85 ± 1% (165 ± 4 beats/min) of maximal heart rate for the control group and 86 ± 1% (139 ± 4 beats/min) for the drug group.

Side effects of drug treatment. Of the six subjects taking propranolol, one noted excessive fatigue during exercise. This symptom gradually dissipated during the 6 week training period. No other side effects were reported.

Effects of training in the control group. Comparison of maximal treadmill performance before and after training in the control group (Tests I and IV) demonstrated a mean increase in maximal oxygen consumption from 47.5 ± 1.1 to 51.4 ± 0.4 ml/kg per min ($p < 0.05$) (Fig. 1 and 2). Exercise duration increased from 18.3 ± 0.7 to 20.7 ± 0.7 minutes ($p < 0.01$) (Fig. 3 and 4). Mean heart rate at rest decreased from 68 ± 5 to 59 ± 3 beats/min, but this change was not statistically significant ($p < 0.09$) (Fig. 5C). Maximal exercise heart rate did not change after training.

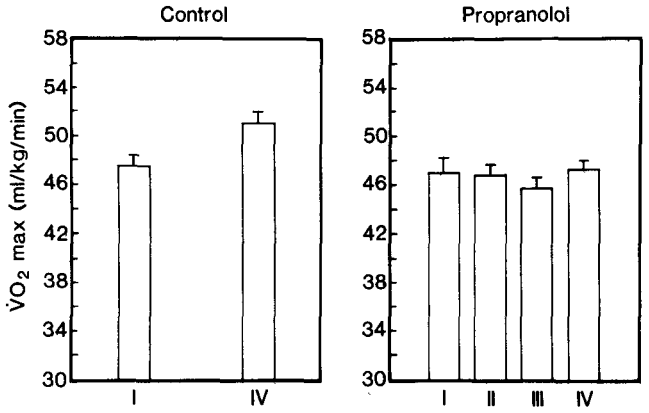


Figure 1. Effect of exercise training on maximal oxygen consumption ($\dot{V}O_2$ max). Brackets represent mean ± standard error. I = exercise test before training or drug; II = test during drug administration before training; III = test during drug administration after training; IV = test without drug after training.

Submaximal heart rate at work loads of 7 METS decreased from 134 ± 4 to 119 ± 3 beats/min ($p < 0.02$, Fig. 5D). Rest systolic and diastolic pressures tended to decrease, but changes were not statistically significant. Some subjects increased their maximal ventilation, but there was not a statistically significant change in this measurement. No significant changes or trends were observed in maximal systolic or diastolic pressure.

Effects of beta-adrenergic blockade before training. After beta-blockade was achieved and before training commenced (Tests I and II), there were significant decreases in mean rest heart rate (70 ± 4 to 57 ± 2 beats/min, $p < 0.05$), maximal heart rate (194 ± 3 to 161 ± 4 beats/min,

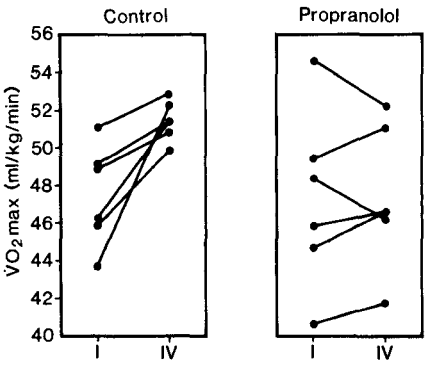
Table 2. Effect of Submaximal Beta-Receptor Blockade on Reduction of Maximal Exercise Heart Rate Before and After Training

	Test II	Test III
Decrease in maximal exercise heart rate (beats/min)	32 ± 4	24 ± 5
Plasma level of propranolol (ng/ml)*	16.5 ± 4.6	17.8 ± 4.9
Time interval between dose and sample (h)	6 3 ± 0.4	6.2 ± 0.3

* Corresponding steady state plasma trough levels obtained before treadmill testing are listed along with dosing interval.

Values are mean ± standard error. Differences between groups are not significant.

Figure 2. Intersubject variability of maximum oxygen consumption ($\dot{V}O_2$ max). Abbreviations as in Figure 1.



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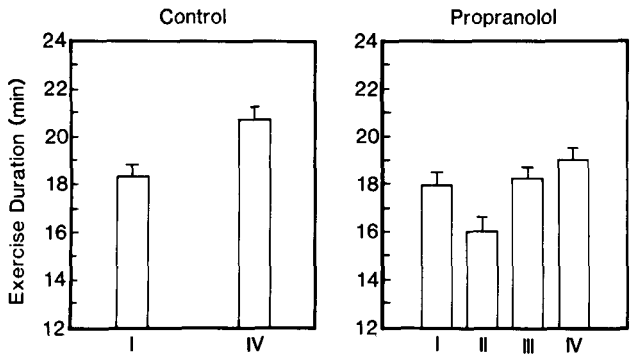


Figure 3. Effect of exercise training on treadmill exercise duration. **Brackets** represent mean ± standard error. Abbreviations as in Figure 1.

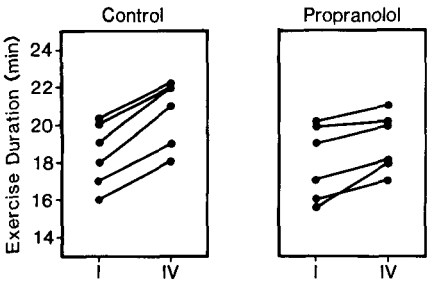
$p < 0.05$) and exercise duration (17.9 ± 0.8 to 16.0 ± 0.6 min, $p < 0.05$). Maximal systolic pressure tended to decrease (200 ± 4 to 183 ± 6 mm Hg), but this decrease was not statistically significant. No significant changes or trends were observed in maximal oxygen consumption, maximal ventilation, maximal diastolic pressure, rest diastolic pressure or rest systolic pressure.

Effects of training in the propranolol group. Comparison of Tests I and IV in the drug group demonstrate the effect of training when the subjects were tested in the absence of beta-adrenergic blockade, first on entry into the study and then at the conclusion of the study after administration of the drug had been stopped. Maximal oxygen consumption did not change from Test I to Test IV (Fig. 1 and 2). No significant difference in maximal oxygen consumption was observed between the control and drug groups before training, but a difference was observed between these groups after training (51.4 ± 0.4 ml/kg per min for control subjects versus 47.4 ± 1.5 ml/kg per min for the propranolol group, $p < 0.05$) (Fig. 5A). Exercise duration in the drug group increased slightly (17.9 ± 0.8 to 19.0 ± 0.6 min, $p < 0.05$) (Fig. 3 and 4). However, a significant difference (+2.3 ± 0.2 min control versus +1.1 ± 0.3 min propranolol, $p < 0.01$) was observed between the two groups after training (Fig. 5B). A significant decrease was observed in mean heart rate at rest (70 ± 4 to 62 ± 2 beats/min, $p < 0.05$) (Fig. 5C) in the propranolol group, a decrease of 13%. However, submaximal heart rate at 7 METS did not change after training ($p = 0.51$) (Fig. 5D). A significant difference was observed in submaximal exercise heart rate between the control and drug groups (−14 ± 4 versus −3 ± 3 beats/min, respectively, $p < 0.05$). No changes were observed in maximal heart rate, maximal diastolic pressure or maximal systolic pressure in the drug group or between control and drug groups.

A comparison of Tests II and III shows the effect of training in the presence of submaximal blockade. Exercise duration increased with training (16.0 ± 0.6 to 18.1 ± 0.5 min, $p < 0.05$) (Fig. 3), but no significant changes were observed in maximal oxygen consumption, maximal ventilation, mean rest heart rate, maximal heart rate or submaximal heart rate.

The effect of submaximal beta-blockade on exercise performance after training is demonstrated by comparing Tests III and IV in the drug group. Maximal heart rate increased from 168 ± 5 to 191 ± 3 beats/min ($p < 0.05$). Mean heart rate at rest was 56 ± 4 beats/min in Test III and 62 ± 2 beats/min in Test IV (p = not significant). Exercise duration improved significantly from 18.1 ± 0.5 to 19.0 ± 0.6 min ($p < 0.05$) (Fig. 3). Maximal ventilation tended to improve (124.0 ± 7.5 to 136.2 ± 6.5 liters/min), but the increase was not significant. No significant changes were noted in maximal oxygen consumption, maximal diastolic pressure, rest systolic pressure or rest diastolic pressure.

Figure 4. Intersubject variability of exercise duration. Abbreviations as in Figure 1.



Discussion

We have shown that low dose beta-adrenergic receptor blockade markedly attenuates the training response to aerobic conditioning in healthy men, as evidenced by lack of improvement in maximal oxygen consumption, relatively small improvement in duration of exercise and lack of change in submaximal exercise heart rate. In contrast, the control group demonstrated an increase in maximal oxygen consumption, a larger increase in exercise duration and a significant decrease in submaximal exercise heart rate.

On comparison of these results with those obtained in our previous study (1) utilizing high dose beta-adrenergic blockade and a similar training regimen (Fig. 6), the only difference between the two treatment groups was a decrease in rest heart rate seen in the group with submaximal beta-blockade. Thus, the group with submaximal beta-blockade had essentially the same attenuated response as did the group with maximal blockade.

Effect of propranolol on exercise training response. Our findings demonstrate that beta-blockade (whether high or low dose) inhibits the training response to aerobic exercise conditioning in normal persons. It has been established that the intensity (that is, in terms of heart rate) of a training program is a major factor that governs the observed training

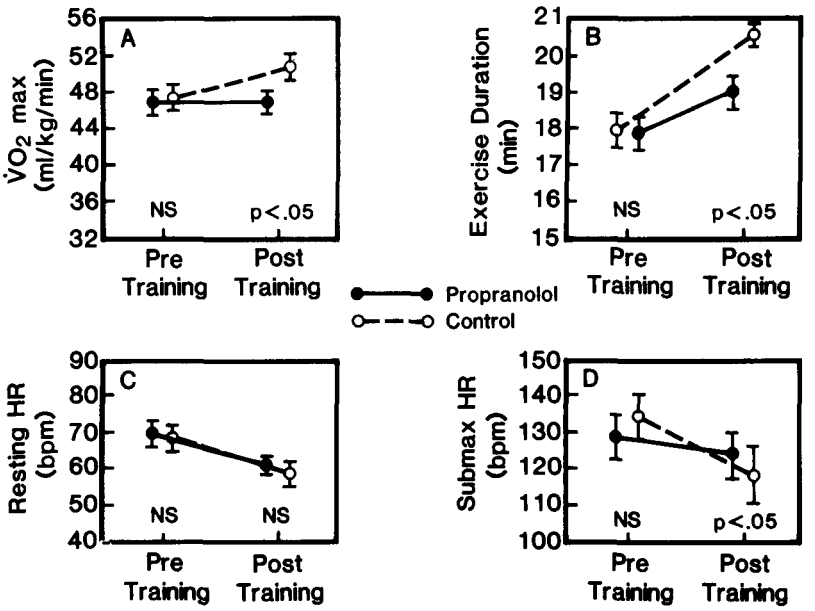


Figure 5. Comparison of the effects of exercise training in the control and propranolol groups. **Brackets** represent mean ± standard error. Before training there were no significant differences for any of the variables. Significant differences between the groups after training are indicated by the p values. Comparison was done by the unpaired two-tailed *t* test. HR = heart rate; NS = not significant; p = probability; submax = submaximal heart rate at work loads of 7 METS; $\dot{V}O_2$ max = maximal oxygen consumption.

response (3). Karvonen (4) stated that a target heart rate of at least 60% of the difference between maximal heart rate and rest heart rate is necessary before a training response is observed in a training program of at least 4 to 5 days per week.

Patients receiving propranolol exercised at less than 60% of this difference while taking the drug. Thus, heart rates during training in the propranolol group were lower than those generally required for training to occur in a typical exercise regimen in unmedicated, normal subjects. A possible reason for the poor training response in our subjects who were taking propranolol was their inability to attain a high enough heart rate during training because of beta-adrenergic receptor blockade. The mechanisms by which conditioning occurs are unknown, but the effect of a high exercise training heart rate would be expected to be a high myocardial oxygen consumption, which may be necessary for cardiac conditioning to occur. Because propranolol prevented a high heart rate during training, it may not have allowed a sufficient increase in myocardial oxygen consumption for cardiac training effects. The small increases in exercise duration after training that were unaccompanied by increases in myocardial oxygen consumption in the propranolol group may reflect some degree of conditioning of skeletal muscle or the peripheral circulation without central cardiac conditioning.

Clinical implications. The findings of these studies should be interpreted only in the context of normal persons without

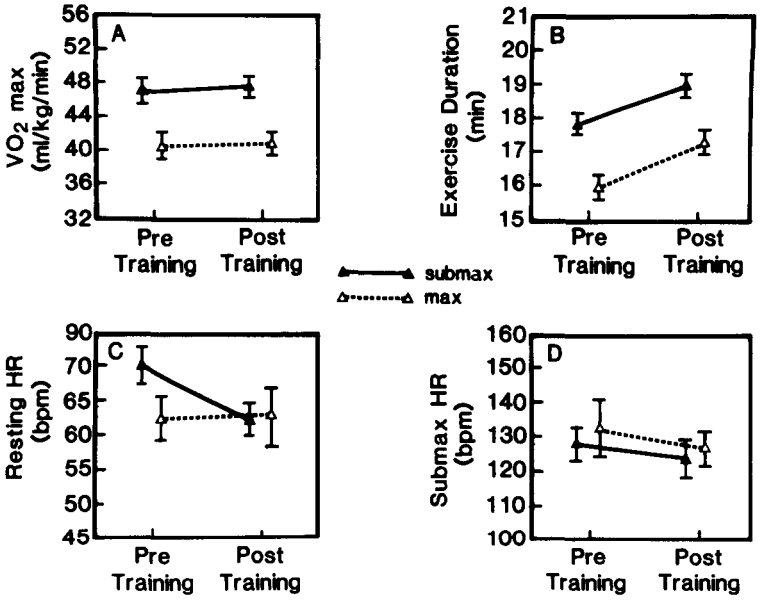


Figure 6. Comparison of the effects of submaximal (50%) and maximal beta-blockade on the training response to aerobic conditioning. Data for maximal blockade from Sable et al. (1). **Brackets** represent mean ± standard error. Max = group with maximal beta-receptor blockade; submax = group with submaximal beta-receptor blockade. Other abbreviations as in Figure 5.

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evidence of coronary artery disease. In a recent study (5), it was concluded that conditioning does occur in patients with coronary artery disease who are under the influence of beta-adrenergic blockade. If this is confirmed, consideration must be given to the possibility that the mechanisms governing the training response in normal persons and those with coronary disease may be different. It would appear from our two studies that the sympathetic nervous system must be intact to produce a training effect in normal persons. In patients with coronary artery disease, myocardial ischemia during exercise may prevent conditioning whether or not beta-blockade is present. Noncardiac effects of training ing may be a major aspect of conditioning in patients with coronary artery disease, and these may be unaffected by beta-blockade.

The lack of training effect in normal subjects taking beta-adrenergic receptor blocking agents may be of clinical significance, regardless of effects of these drugs in patients with coronary artery disease. Many persons without coronary disease may continue taking beta-adrenergic receptor blocking agents and undergo exercise training as part of preventive health programs. These would include subjects with arrhythmias or hypertension, which are common in the absence of coronary disease. If our results in normal subjects can be extrapolated to such persons, they may not gain the usual cardiovascular conditioning effects with standard exercise regimens.

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